

ARTICLE

The Mechanochemical Fries Rearrangement: Manipulating Isomer Ratios in the Synthesis of *p*-Hydroxyacetophenone at Different Scales

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Here, we present the first mechanochemical Fries rearrangement for the industrially important synthesis of para-hydroxyacetophenone, inside a ball mill and a twin-screw extruder. Our approach leads to quantitative conversion in as little as 90 minutes. Furthermore, the utilisation of liquid-assisted grinding can shift the isomer ratio resulting in an excess of the desired para-product. The multigram scale-up via a continuous extrusion process leads to similar results in only three minutes of residence time while completely avoiding solvents. The extrusion temperature of 75–100 °C can even further be reduced by combining extrusion at 50 °C with a subsequent ageing step.

Introduction

Hydroxyaryl ketones are synthetically important compounds with applications in the pharmaceutical and cosmetic industry.¹ The most common method for their preparation is the Fries rearrangement (**Figure 1A**), rendering a facile reaction pathway of high atom economy to access hydroxyaryl ketones from aromatic esters.^{1–4} This acid-mediated reaction can be carried out with either Lewis-, Brønsted-, or solid-acids, both, in the liquid- and the gas phase.^{5–8} The latter requires high temperatures, not only favouring the deactivation of the catalysts by coking but also leading to poorer product selectivity compared to liquid-phase reactions.^{7,9} Said selectivity is a major issue since both *p*- and *o*-isomers are formed. Their ratio strongly depends on the reaction temperature and the type and polarity of the solvent. While low temperatures and polar solvents preferentially lead to the *p*-isomer, high temperatures and nonpolar solvents or even solvent-free approaches lead to the *o*-isomer.^{4,5,7,9,10} The Fries rearrangement of phenyl acetate (PA), thus, leads to *para*-hydroxyacetophenone (*p*-HAP) and *ortho*-hydroxyacetophenone (*o*-HAP). While *o*-HAP is of minor importance in the production of fine chemicals and pharmaceuticals, *p*-HAP is the economically most important hydroxyaryl ketone, produced in quantities of 1.000 to 10.000 tons per year in the European Union alone.¹¹ Accordingly, it is desirable to influence the isomer ratio and shift it in favour of *p*-HAP while at the same time getting rid of the large amounts of toxic solvents and acids commonly utilized (e.g., hydrofluoric

acid). The elimination or reduction of these hazardous chemicals would be highly desirable in the context of green chemistry (**Figure 1B**).

Mechanochemistry, comprising chemical reactions that are initiated by mechanical forces, is a possible solution to solve these issues. Due to its inherent solvent-free character, it is gaining increasing attention as a sustainable alternative to conventional solvent-based reactions.^{12,13} Mechanochemistry has been used for the synthesis of a variety of compounds such as organic^{14–17}, inorganic¹⁸, or polymer¹⁹ materials and has demonstrated the potential of altering product selectivity and even accessing novel compounds.^{20–23} While scarce, some other molecular rearrangements have also been reported.^{24,25}

Typically, mechanochemical reactions are carried out in ball mills in which colliding milling balls provide the mechanical energy for the reaction. However, this is not suitable for larger quantities. At the same time, the drawbacks of ball milling, namely poor temperature and reaction control as well as discontinuous operation prevent the widespread use of this technology in the industry. As a continuous alternative, mechanochemical extrusion has recently provided promising results.^{26,27} Extruders have broad applications in a range of industries from food and polymers to pharmaceuticals. The small diameter of extruder barrels compared to their length allows for precise temperature and reaction control along the length of the barrel.²⁸ Due to its continuous operation,

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

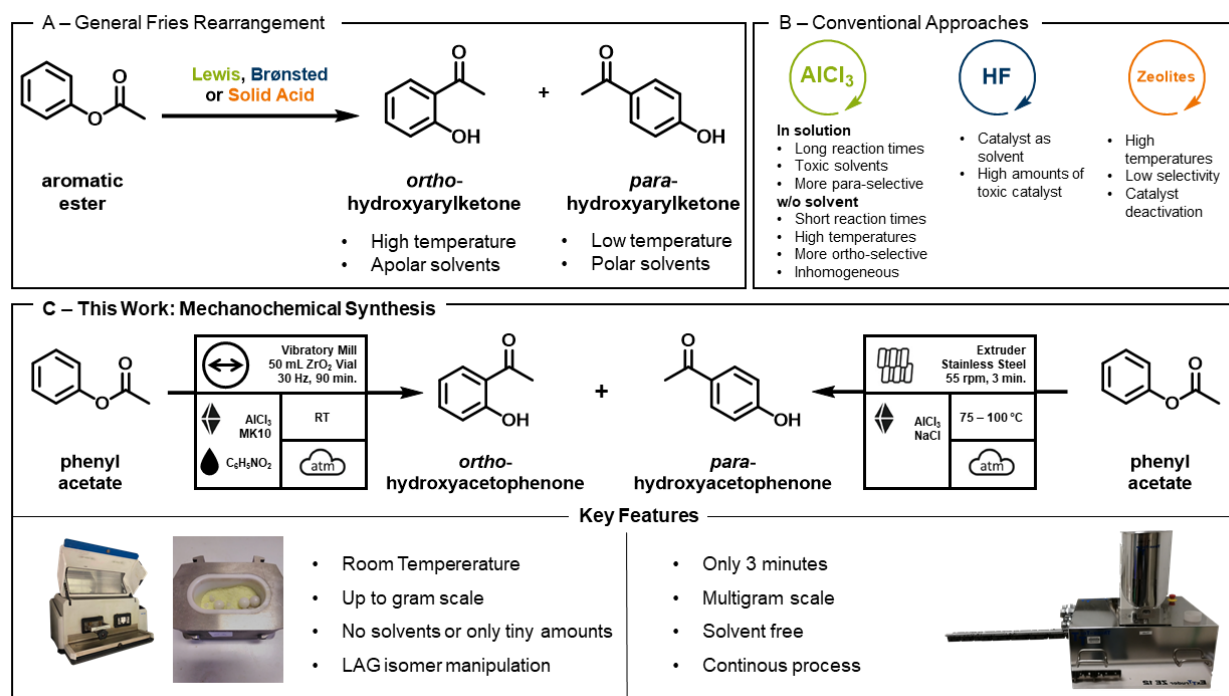


Figure 1: Preparation of hydroxyacetophenones via the Fries rearrangement. A: General scheme of the Fries rearrangement of aromatic esters. The reaction can be carried out with Lewis, Brønsted or solid acids. B: Conventional mediators in the Fries rearrangement with their characteristics. C: The first mechanochemical Fries rearrangement with its key features in both ball mill and extruder.

extrusion is the mechanochemical embodiment of flow chemistry and allows large-scale operation.^{28,29} So far, twin screw extruders were used to synthesize metal-organic frameworks³⁰, dyes³¹, pharmaceuticals³², small organic molecules^{33,34}, and polymers.³⁵ Recently, we reported on the first example of a rearrangement reaction via extrusion and showed how crucial temperature control is for this process.³⁶ Here, we present the first mechanochemical Fries rearrangement and use it to prepare *para*-hydroxyacetophenone. We first optimise the reaction in the ball mill and then scale it up to a continuous process in an extruder (Figure 1C).

Results and Discussion

Reaction Development in the Ball Mill

We began our investigation using phenyl acetate (PA), three equivalents of AlCl₃ and 2.5 g NaCl as bulk material in a vibratory ball mill (MM500, RETSCH GmbH) at a milling frequency of 30 Hz, a reaction time of 90 minutes, in a 50 mL ZrO₂ milling vessel with 25 ZrO₂ milling balls (10 mm). This experiment was repeated in triplicate to ensure the reproducibility of our reaction. Under these conditions, a conversion of PA of 33 % was observed according to ¹H-NMR spectroscopy (Table 1, entry 1). Based on this result, we varied the milling frequency, the reaction time, the AlCl₃ equivalents and the milling material. Increasing the amount of AlCl₃ accelerates the reaction (Table 1, entries 2-4). With eight equivalents, a conversion of almost 90 % can be observed after 90 minutes. Therefore, to investigate the reaction time we used 5.5 equivalents of AlCl₃. With this amount, an almost complete conversion of PA can be

Table 1: Reaction conditions and conversion of the Fries rearrangement of PA. Reaction conditions, unless otherwise stated: 1 mL PA, 2.5 g NaCl, MM500, 50 mL milling vessels with 25 milling balls (10 mm) of the same material. SS = Stainless steel. The grey highlighting indicates the optimized parameters.

Entry	Milling Material	Frequency (Hz)	Time (min.)	Eq. AlCl ₃	Conversion (%) ^a
1	ZrO ₂	30	90	3	33±2 ^b
2	ZrO ₂	30	90	5.5	72
3	ZrO ₂	30	90	8	88
4	ZrO ₂	30	90	8 ^c	36
5	ZrO ₂	30	300	5.5	87
6	ZrO ₂	30	480	5.5	93
7	ZrO ₂	20	480	5.5	69
8	SS	30	90	3	8
9	SS	30	90	5.5	56

^a determined with ¹H-NMR spectroscopy. ^b The reaction was carried out in triplicate and the deviation from the mean value is given. ^c To keep the amount of reactants in the milling vessel constant, the amount of PA was reduced to 346 µL.

observed after 480 minutes. If the milling frequency is reduced from 30 to 20 Hz, the conversion also drops sharply (Table 1, entries 5-7). Thus, we were able to achieve quantitative conversion of PA, but we needed either a large excess of AlCl₃ or long reaction times. To avoid this, we investigated the use of stainless steel as a milling material. This is denser than ZrO₂ and provides more energy for the reaction. (Table 1, entries 8 and 9). Compared to ZrO₂, the yield decreased. This may be the result of a reaction of the corrosive AlCl₃ with the steel surface

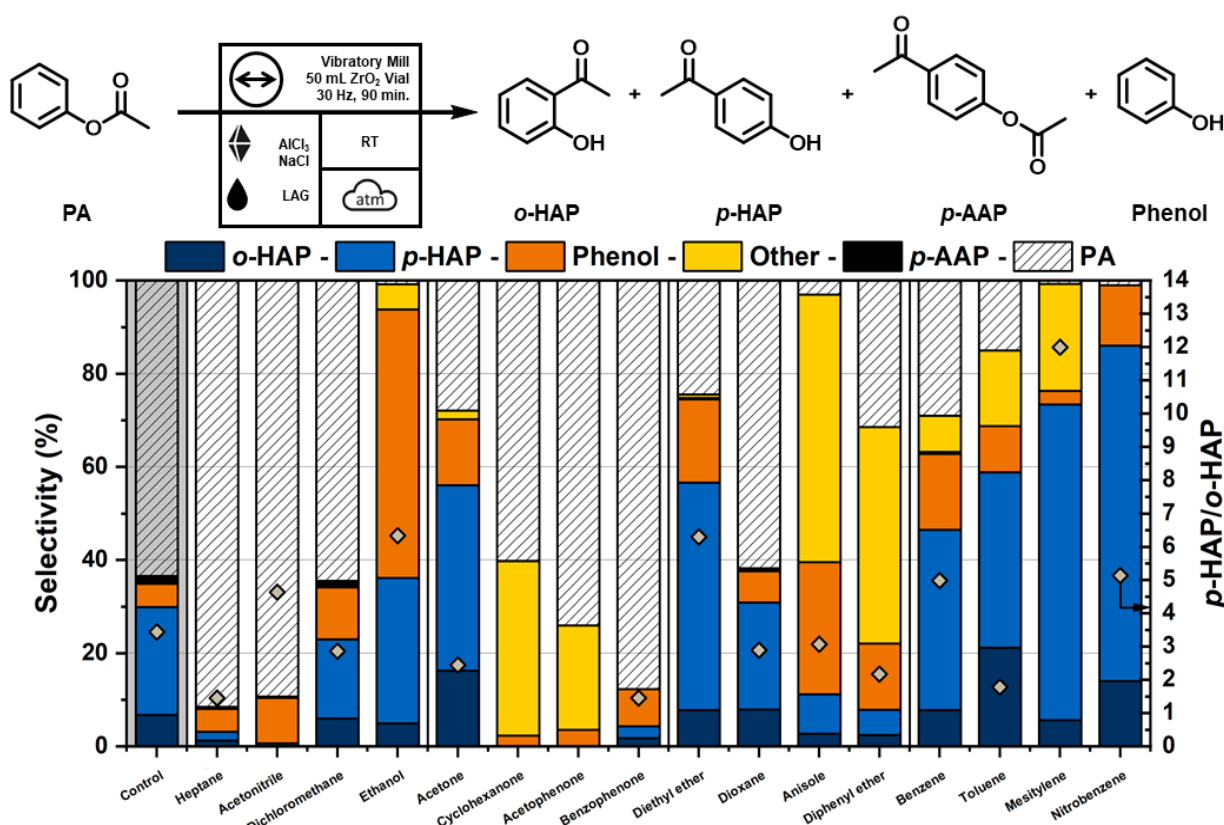


Figure 2: Top: The acid-mediated Fries rearrangements of phenyl acetate (PA) to the two products *o*- and *p*-hydroxyacetophenone (*o*-HAP and *p*-HAP, respectively) and to the by-products *p*-acetoxyacetophenone (*p*-AAP) and phenol. Bottom: The selectivity (determined with GCMS) of the mechanochemical Fries rearrangement using different LAG additives. The beige diamonds indicate the ratio of the two products *p*- and *o*-HAP. Reaction conditions: 1 mL PA, 3.14 g AlCl₃, 2.5 g NaCl, 671 μ L of solvent, MM500, 30 Hz, 90 min. reaction time, 50 mL ZrO₂ milling vessel with 25 ZrO₂ milling balls (10 mm).

which subsequently reduces the number of acid molecules available for reaction.

In the next step, we investigated the addition of various additives to the reaction to shorten the reaction time while keeping the required amount of AlCl₃ low. It is known that the addition of small amounts of solvent can have a profound influence on mechanochemical reactions. The added amount of solvent is not sufficient to dissolve the reactants but supports the mixing. This is called liquid-assisted grinding (LAG) and is characterized by the η -coefficient, which is the amount of solvent in μ L divided by the mass of the reaction mixture in mg. Within this study, we analyzed the product distribution by GCMS and investigated the influence of the different additives on the formation of *p*-HAP (Figure 2). The reference point for this study was the same as before (Table 1, entry 1 and Figure 2, control). The product distribution is composed of the two products of the Fries rearrangement, while small amounts of phenol and *p*-acetoxyacetophenone (*p*-AAP) were also observed. The isomer ratio of *p*-HAP to *o*-HAP (*p/o*-ratio) was 3.4. A wide range of different solvents was investigated. Ketones, ethers and aromatic compounds led to the highest conversions to the desired products. Therefore, we investigated these in more detail. Acetone showed a conversion of about 70 % with few by-products with a *p/o*-ratio of 2.4. The use of larger ketones led mainly to by-products attributable to an aldol reaction. Among the ethers, diethyl ether showed a similar

performance to acetone. Larger ethers showed little change from the reference or showed mainly phenol and the products of a competitive Friedel-Crafts acylation. Finally, we turned to aromatic compounds. Benzene and toluene showed similar activity in the reaction with conversions of 70 % and 80 %, respectively, and small amounts of by-products due to Friedel-Crafts acylation. Quantitative conversion was obtained with mesitylene, and the reaction mixture consisted mainly of the products of the Fries rearrangement with a high *p/o*-ratio of about 12. To avoid electrophilic substitutions as side reactions, we investigated the addition of deactivated nitrobenzene to the reaction. This led to a similar conversion compared to mesitylene but with a complete absence of side products apart from a small amount of phenol while the isomer ratio showed a strong excess of *p*-HAP. After chromatographic purification of this reaction, the products were obtained in an overall yield of 71 % (Figure 3, column 2). The desired *p*-HAP accounted for 63 %.

The last optimization step focused on the rheology of the reaction mixture. In mechanochemical reactions, it is important to ensure that a powdery reaction mixture is present throughout the reaction. This is advantageous for reproducibility and mechanical energy transfer. Using NaCl, we often obtained hard, solidified melts. After an investigation of different bulk materials, we identified Montmorillonite K10 (MK10) as suitable (See ESI section 1.1 for more information on

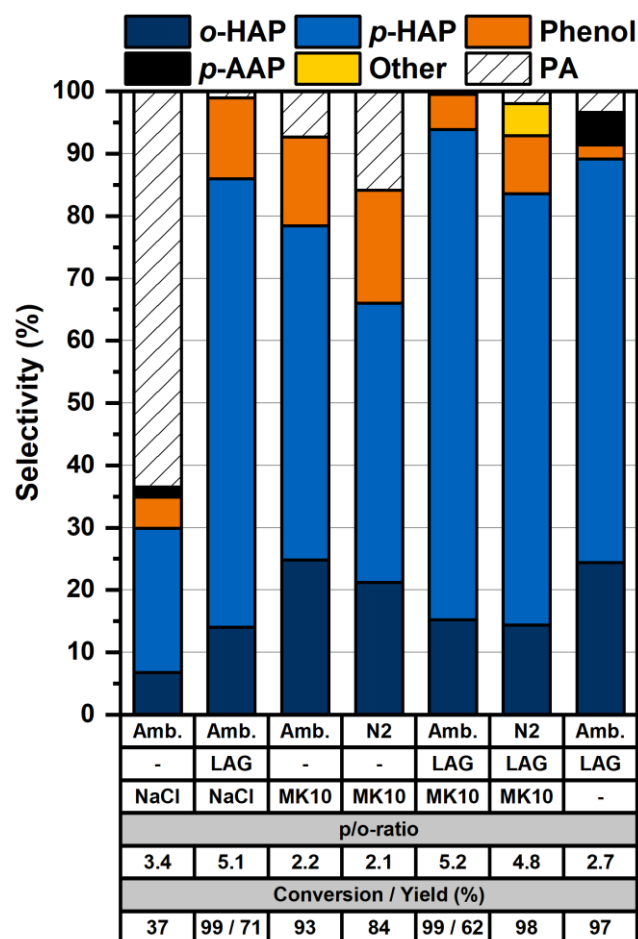


Figure 3: Reaction conditions, conversions, and ratios of *p*-HAP to *o*-HAP in the Fries rearrangement of PA. Reaction conditions, unless otherwise stated: 1 mL PA, 3.14 g AlCl₃, nitrobenzene as LAG-additive ($\eta = 0.1$), 2.5 g NaCl or 6.12 g of MK10. MM500, 30 Hz, 50 mL milling vessels with 25 milling balls (10 mm) of the same material. The LAG value was calculated by dividing the amount of nitrobenzene in μ L by the total mass of the remaining reaction mixture in mg. The reactions were analyzed by GCMS.

the bulk materials studied). With MK10, we were able to achieve a similar performance as in the reference reaction. At the same time, the reaction mixture remained a powder (Figure 3, columns 2 and 5).

In the next step, we conducted control experiments (Figure 3). If no LAG additive is used, a quantitative conversion after 90 min. can be found with MK10 alone. This contrasts with the initial results where under the same conditions without LAG and with NaCl only a 37 % conversion was found. We attribute this to insufficient mixing since the crude reaction mixture after the reaction was often a solidified mass and not a powder. The control experiments now allow the conclusion that both LAG and MK10 support the mixing of the reaction and one of them is sufficient to prevent solidification of the reaction mixture and thus accelerate the conversion. Interestingly, the amount of *p*-HAP in the product mixture decreases drastically when no LAG is used. This is consistent with conventional chemistry, in which the *o*-isomer is preferably formed in the absence of solvents. If the bulk material is omitted, complete conversion can be observed with a significantly lower *p/o*-ratio than under the

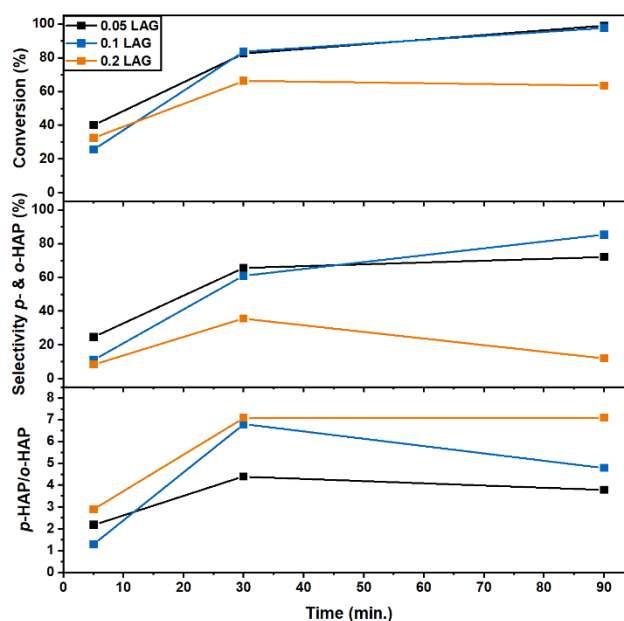


Figure 4: Reaction kinetics of the mechanochemical Fries rearrangement for different amounts of LAG. Reaction conditions, unless otherwise stated: 1 mL PA, 3.14 g AlCl₃, 6.12 g MK10 and nitrobenzene as liquid additive. MM500, 30 Hz, 50 mL milling vessels with 25 milling balls (10 mm) of the same material. The reactions were analyzed by GCMS. Top: conversion of the reaction. Middle: Selectivity to the *p*-HAP and *o*-HAP. Bottom: Ratio of the two product isomers.

optimized conditions. Since AlCl₃ reacts strongly with moisture, we carried out experiments under a nitrogen atmosphere. We found similar conversions as under air. Thus, we can manipulate the isomer ratio of the products in our reaction by the type and amount of liquid additive used, as well as by the bulk material.

Lastly, we investigated the influence of the LAG quantity on the reaction time (Figure 4). For this purpose, we used the optimized conditions with MK10 (Figure 3, column 5). We examined η -values of 0.05, 0.1 and 0.2 at 5 min., 30 min., and 90 min. We found that both the conversion and the selectivity to the products of the Fries rearrangement at 0.05 is comparable to that at 0.1, while it decreases at 0.2. Furthermore, we found that the higher the η -value, the more *p*-HAP is formed. From this, we conclude that with 0.1 we have hit a sweet spot³⁷ with which we can achieve both high conversion and selectivity while also predominantly forming the desired *p*-HAP.

Transfer to a continuous process

With this knowledge, we set out to transfer the reaction into a continuous extrusion process. For this, AlCl₃ and NaCl were mixed in a 1.25:1 mass ratio and manually fed into the extruder, while PA and the LAG agent were mixed in a 1.5:1 volume ratio and fed with a peristaltic pump (values corresponding to Figure 3, column 2). This allows for precise control of flow rates. The mixture was then extruded at 55 rpm leading to a retention time of three minutes in the extruder. Based on our results in the ball mill, we investigated extrusions with mesitylene, and nitrobenzene as well as without LAG. When using nitrobenzene as LAG no reactivity to the desired products was observed until

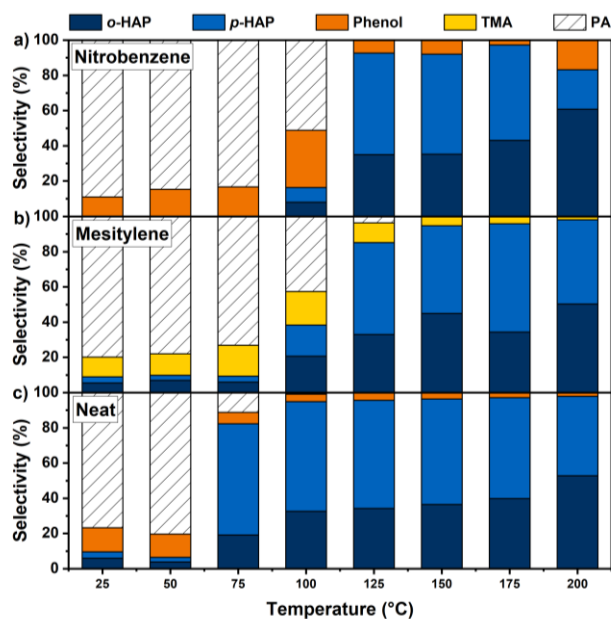


Figure 5: Temperature dependency of selectivity during extrusion with and without LAG. a) LAG with 0.245 mL/min nitrobenzene (top), b) LAG with 0.245 mL/min mesitylene (middle), c) no LAG (bottom). Reaction conditions: 0.365 mL/min PA, 4.6 g/min AlCl_3 and 1.8 g/min NaCl feed at a screw speed of 55 rpm. PA = Phenyl acetate, *p*-HAP = *p*-Hydroxy acetophenone, *o*-HAP = *o*-Hydroxy acetophenone, TMA = Trimethyl acetophenone.

100 °C (Figure 5a). This increased sharply at 125 °C to full conversion to *p*-HAP, *o*-HAP, and a small amount of phenol. Here, we reached a *p/o*-ratio of a maximum of 1.6. As expected, the selectivity is strongly temperature-dependent, with higher temperatures favouring the formation of *o*-HAP. Due to the higher reaction temperature, the *p/o*-ratio in the extruder is therefore generally lower than in the ball mill experiments. When replacing nitrobenzene with mesitylene, a similar trend was observed (Figure 5b). Here, the *p/o*-ratio reached a maximum of 1.8 at 175 °C. Phenol was not observed, however, the acylation product of mesitylene occurred. We then went on to omit LAG to find a more favourable rheology with higher torques imbued by the extruder onto the reaction mixture. This was mirrored by the increased reactivity, with about 60 % conversion to *p*-HAP at 75 °C and almost complete conversion at 100 °C (Figure 5c; Table 2, entries 1 and 2). A maximum *p/o*-ratio of 3.3 was achieved at 75 °C. This decreased again with increasing temperature. Overall, in extrusion, the effect of rheology seems to far outweigh the directing properties of LAG agents. To accommodate this, we opted to add 5 % of MK10 to the reaction mixture to achieve a higher viscosity mixture. Yet, in this case, the reaction to the desired product was almost completely suppressed (Table 2, entries 3 and 4). These findings can be explained by rheology and mixing phenomena. The rheology without LAG is more advantageous since the reaction mixture is less liquid and mechanical forces can be better transferred from the extruder screws to the mixture. In contrast to the ball mill, LAG is not needed since the extruder itself sufficiently supports the mixing. Instead, it is possible to perform the Fries rearrangement in only three minutes while the *p/o*-ratio can be mainly influenced by the temperature. This

Table 2: Reaction conditions, conversions, and ratios of *p*-HAP to *o*-HAP in the continuous mechanochemical Fries rearrangement of PA. Reaction conditions unless otherwise stated: 0.365 mL/min PA, 0.245 mL/min LAG, 4.6 g/min AlCl_3 and 1.8 g/min NaCl feed at a screw speed of 55 rpm. Montmorillonite K10 was fed with 0.32 g/min. n = nitrobenzene, m = mesitylene, MK10 = Montmorillonite K10. The grey highlighting indicates the optimized parameters.

Entry	Temperature (°C)	Bulk	LAG	Conv. (%) ^a	<i>p/o</i> ^a
1	75	NaCl	-	89	3.3
2	100	NaCl	-	99 (76)	1.9
3	100	NaCl + 5% MK10	n	14	-
4	100	NaCl + 5% MK10	m	12	0.9
6 ^b	50	NaCl	-	93	2.7

^a determined with GCMS. Yield of *p*-HAP and *o*-HAP in parentheses. ^b samples were extruded and aged at room temperature for 168 h before being quenched.

allows *p*-HAP to be produced on a multigram scale while solvents can be avoided entirely.

It is even possible to lower the reaction temperature further by combining extrusion at 50 °C with an ageing step. After one week of ageing, the conversion is over 90 % with a *p/o*-ratio of 2.7 (Table 2, entry 6). Thus, we have developed two complementary strategies. It is either possible to achieve full conversion in a reaction time of only three minutes at 100 °C with a *p/o*-ratio close to 2 or alternatively to combine extrusion at 50 °C with a one-week ageing step to achieve a ratio close to 3.

Environmental Impact

To verify the ecological benefit we evaluated our process, a solution-based route⁶ and an industrial HF-catalysed process³⁹ using the Eco-scale proposed by van Aken *et al.* (Table 3).³⁸ Here, the HF catalysed reaction scored lowest, mainly because of safety penalties. The solution-based process receives 20 penalty points in this category as well, because a range of different solvents are used. This process gets 54 points on the Eco-scale. Ball milling results in similar yield, however, safety is improved by choosing this route resulting in fewer penalty

Table 3: Calculation of Eco-scale.³⁸ Additionally, the reaction time was taken into account.

Penalty points	Solution	Industrial HF	Ball mill	Extrusion
Yield	14	4.5	14.5	12
Price ^[a]	5	3	5	3
Safety	20	25	10	0
Technical Setup	2	6	2	2
Temperature/Time	3	8	0	2
Workup ^[b]	2	4	6	6
Total	46	50.5	37.5	25
Eco-Scale	54	49.5	62.5	75
Reaction time [h]	26	1.7	1.5	0.05

^[a] Price of reaction components for 10 mmol of product. ^[b] All pathways arrive at a mixture of *o*- and *p*-product.

points in this category. Additionally, the time consumed in the reaction is significantly lower than the solution-based route. Much better is the extrusion process with the highest score on the Eco-scale and the lowest reaction time by far, scoring in at a total of 75 out of 100 points in the ranking with a residence time of barely 3 minutes.

Conclusion

In summary, we performed the first mechanochemical Fries rearrangement and evaluated the optimal milling conditions. It was found that the amount of AlCl_3 used had the greatest influence on the reaction, followed by the reaction time and the milling frequency. We investigated the addition of small amounts of solvents to the reaction and found that the reaction time can be drastically reduced by liquid-assisted grinding. Furthermore, it is possible to manipulate the p/o ratio by changing the liquid additive or the bulk material. With nitrobenzene, the reaction was carried out with almost complete avoidance of by-products and the desired p -HAP was obtained in a yield of 63 %. The yield is 71 % if o -HAP is considered. Subsequently, we transferred our reaction into a continuous process in a twin-screw extruder and investigated the influence of LAG, bulk material, and temperature on the reaction. It was found that LAG in the extruder is not beneficial since the extruder itself sufficiently mixes the reaction. Instead, the reaction temperature was found to be the crucial parameter for this reactor. In the extruder, the highest p/o -ratio of 3.3 is achieved at 75 °C while full conversion is achieved at 100 °C. Thus, we can prepare p -HAP in 61 % yield on a multigram scale in the extruder in only three minutes while completely avoiding solvents. This makes the herein presented process a sustainable alternative to established processes for the synthesis of the economically important p -HAP.

Author Contributions

D. M. B., T. R., K. B. and V. P. performed mechanochemical syntheses and sample purification. D. M. B. performed sample analysis. T. R. performed environmental analysis. D. M. B., T. R., S. G. and L. B. prepared the manuscript. L. B. coordinated and supervised the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the Federal Ministry of Education and Research (BMBF) for support of the Mechanocarb project (award number 03SF0498).

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